

PCT

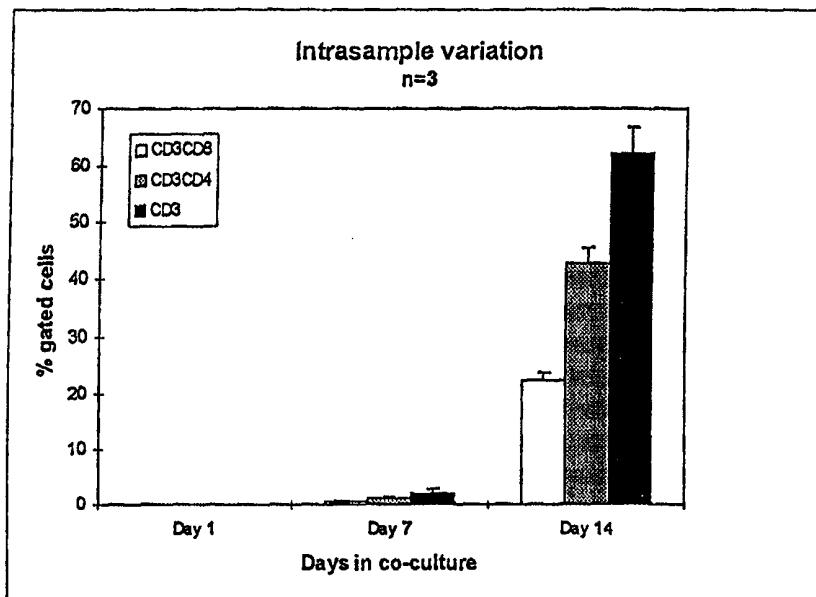
WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ :	A3	(11) International Publication Number:	WO 00/27999
C12N 5/06, 5/08, A61L 27/38		(43) International Publication Date:	18 May 2000 (18.05.00)
(21) International Application Number:	PCT/US99/26795	(81) Designated States:	AU, CA, CN, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(22) International Filing Date:	12 November 1999 (12.11.99)	Published	<i>With international search report.</i>
(30) Priority Data:	60/107,972 12 November 1998 (12.11.98) US	(88) Date of publication of the international search report:	3 August 2000 (03.08.00)
(71) Applicants (for all designated States except US):	CYTOMATRIX, LLC [US/US]; 50 Cummings Park, Woburn, MA 01801 (US). THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US).		
(72) Inventors; and			
(73) Inventors/Applicants (for US only):	ROSENZWEIG, Michael [US/US]; Cytomatrix, LLC, 50 Cummings Park, Woburn, MA 01801 (US). PYKETT, Mark, J. [US/US]; Cytomatrix, LLC, 50 Cummings Park, Woburn, MA 01801 (US). SCADDEN, David, T. [US/US]; Massachusetts General Hospital East, 13th Street, Building 149, Charlestown, MA 02129 (US). POZNANSKY, Mark, C. [US/US]; Massachusetts General Hospital East, 13th Street, Building 149, Charlestown, MA 02129 (US).		
(74) Agent:	GATES, Edward, R.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).		

(54) Title: LYMPHOID TISSUE-SPECIFIC CELL PRODUCTION FROM HEMATOPOIETIC PROGENITOR CELLS IN THREE-DIMENSIONAL DEVICES



(57) Abstract

The invention relates to a method for lymphoid tissue-specific cell production from hematopoietic progenitor cells in unique, three-dimensional culture devices, in the presence of lymphoreticular stromal cells and in the absence of exogenously added growth factors. The resulting differentiated progeny. The lymphoid tissue-specific cells may be isolated at any sequential stage of differentiation and further expanded. The lymphoid tissue-specific cells also may be genetically altered at any stage of the process.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/26795

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C12N5/06	C12N5/08	A61L27/38
-------	----------	----------	-----------

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>NAUGHTON G ET AL: "Three-dimensional bone marrow cell and tissue culture system" BIOTECHNOLOGY ADVANCES, GB, ELSEVIER PUBLISHING, BARKING, vol. 15, no. 2, 1 January 1997 (1997-01-01), page 401 XP004073886 ISSN: 0734-9750 the whole document</p> <p>-----</p>	1-85
X	<p>EP 0 358 506 A (MARROW TECH INC) 14 March 1990 (1990-03-14) abstract page 3, line 5 -page 3, line 40; claims 1-133</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-85

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

15 May 2000

Date of mailing of the international search report

25 May 2000 (25.05.00)

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Meyer, W

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/26795

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 443 950 A (NAUGHTON GAIL K ET AL) 22 August 1995 (1995-08-22) abstract ---	1-85
X	EP 0 241 578 A (MARROW GROUP INT) 21 October 1987 (1987-10-21) abstract; claims 1-8 ---	1-85
X	US 5 580 781 A (NAUGHTON GAIL K ET AL) 3 December 1996 (1996-12-03) abstract; page 3, line 34 -page 4, line 21; claims 1-50 ---	1-85
X	WO 90 15877 A (UNIV MICHIGAN) 27 December 1990 (1990-12-27) abstract; claims 1-19 ---	1-85
X	NAUGHTON B A ET AL: "A THREE-DIMENSIONAL CULTURE SYSTEM FOR THE GROWTH OF HEMA-TOPOIETIC CELLS" PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, US, NEW YORK, NY, vol. 333, 1990, pages 435-445, XP000881141 ISSN: 0361-7742 the whole document ---	1-31
X	ROSENZWEIG M ET AL: "Enhanced maintenance and retroviral transduction of primitive hematopoietic progenitor cells using a novel three-dimensional culture system" GENE THERAPY, GB, MACMILLAN PRESS LTD., BASINGSTOKE, vol. 4, no. 9, 1 September 1997 (1997-09-01), pages 928-936, XP002091698 ISSN: 0969-7128 abstract ---	1-85
A	BAGLEY J ET AL: "LONG-TERM THREE DIMENSIONAL HEMATOPOIETIC STEM CELL CULTURE" AMERICAN CHEMICAL SOCIETY. ABSTRACTS OF PAPER. AT THE NATIONAL MEETING, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 216, no. 1/03, 1998, page BIOT129 XP000881132 ISSN: 0065-7727 abstract ---	1-85
		-/-

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/26795

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BAGLEY J ET AL: "EXTENDED CULTURE OF MULTIPOTENT HEMATOPOIETIC PROGENITORS WITHOUT CYTOKINE AUGMENTATION IN A NOVEL THREE-DIMENSIONAL DEVICE" EXPERIMENTAL HEMATOLOGY, US, NEW YORK, NY, vol. 27, no. 3, March 1999 (1999-03), pages 496-504, XP000881139 ISSN: 0301-472X the whole document -----	1-85

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/US 99/26795

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 32-42 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

It National Application No

PCT/US 99/26795

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0358506	A	14-03-1990	US 4963489 A		16-10-1990
			US 5032508 A		16-07-1991
			AU 644578 B		16-12-1993
			AU 4211489 A		02-04-1990
			BR 8907642 A		20-08-1991
			CA 1335657 A		23-05-1995
			DK 40591 A		07-05-1991
			HU 56393 A		28-08-1991
			IL 91536 A		31-10-1996
			JP 4501657 T		26-03-1992
			KR 156571 B		15-10-1998
			KR 156684 B		15-10-1998
			KR 156685 B		15-10-1998
			NO 910787 A		22-04-1991
			NZ 230572 A		23-12-1993
			PT 91676 A		30-03-1990
			WO 9002796 A		22-03-1990
			US 5443950 A		22-08-1995
			US 5962325 A		05-10-1999
			US 5460939 A		24-10-1995
			US 5510254 A		23-04-1996
			US 6022743 A		08-02-2000
			US 5580781 A		03-12-1996
			US 5516680 A		14-05-1996
			US 5512475 A		30-04-1996
			US 5541107 A		30-07-1996
			US 5516681 A		14-05-1996
			US 5578485 A		26-11-1996
			US 5785964 A		28-07-1998
			US 5518915 A		21-05-1996
			US 5624840 A		29-04-1997
			US 5902741 A		11-05-1999
			US 5863531 A		26-01-1999
			US 5266480 A		30-11-1993
			US 5160490 A		03-11-1992
			US 5849588 A		15-12-1998
			US 5858721 A		12-01-1999
			ZA 8906886 A		27-06-1990
US 5443950	A	22-08-1995	US 5266480 A		30-11-1993
			US 5032508 A		16-07-1991
			US 4963489 A		16-10-1990
			US 4721096 A		26-01-1988
			US 5962325 A		05-10-1999
			US 5460939 A		24-10-1995
			US 5510254 A		23-04-1996
			US 6022743 A		08-02-2000
			US 5580781 A		03-12-1996
			US 5516680 A		14-05-1996
			US 5512475 A		30-04-1996
			US 5541107 A		30-07-1996
			US 5516681 A		14-05-1996
			US 5578485 A		26-11-1996
			US 5785964 A		28-07-1998
			US 5518915 A		21-05-1996
			US 5624840 A		29-04-1997
			US 5902741 A		11-05-1999
			US 5863531 A		26-01-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/26795

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5443950	A	US	5849588 A	15-12-1998
		US	5858721 A	12-01-1999
		AU	644578 B	16-12-1993
		AU	4211489 A	02-04-1990
		BR	8907642 A	20-08-1991
		CA	1335657 A	23-05-1995
		DK	40591 A	07-05-1991
		EP	0358506 A	14-03-1990
		HU	56393 A	28-08-1991
		IL	91536 A	31-10-1996
		JP	4501657 T	26-03-1992
		KR	156571 B	15-10-1998
		KR	156684 B	15-10-1998
		KR	156685 B	15-10-1998
		NO	910787 A	22-04-1991
		NZ	230572 A	23-12-1993
		PT	91676 A	30-03-1990
		WO	9002796 A	22-03-1990
		US	5160490 A	03-11-1992
		ZA	8906886 A	27-06-1990
		AT	127692 T	15-09-1995
		AU	6815990 A	14-03-1991
		AU	6816090 A	14-03-1991
		AU	615414 B	03-10-1991
		AU	7356887 A	09-11-1987
		BG	51337 A	15-04-1993
		BR	8707673 A	15-08-1989
		CA	1310926 A	01-12-1992
		DE	3751519 D	19-10-1995
		DK	665687 A	17-12-1987
		EP	0309456 A	05-04-1989
		FI	884783 A	17-10-1988
		HK	1007684 A	23-04-1999
		HU	48112 A	29-05-1989
		JP	62249926 A	30-10-1987
		JP	10114664 A	06-05-1998
		JP	1503195 T	02-11-1989
		JP	2857392 B	17-02-1999
		KR	142885 B	15-07-1998
		NO	179181 B	13-05-1996
		NZ	218282 A	28-05-1990
		NZ	220038 A	28-08-1990
		RO	106655 A	30-06-1993
		US	4721096 A	26-01-1988
EP 0241578	A	21-10-1987	AT	127692 T
			AU	595813 B
			AU	5985086 A
			AU	6815990 A
			AU	6816090 A
			AU	615414 B
			AU	7356887 A
			BG	51337 A
			BR	8707673 A
			CA	1282725 A
			CA	1310926 A
			DE	3751519 D
			DK	665687 A
			EP	0309456 A
			FI	884783 A
			HK	1007684 A
			HU	48112 A
			JP	62249926 A
			JP	10114664 A
			JP	1503195 T
			JP	2857392 B
			KR	142885 B
			NO	179181 B
			NZ	218282 A
			NZ	220038 A
			RO	106655 A
			US	4721096 A

INTERNATIONAL SEARCH REPORT

Information on patent family members

I. International Application No

PCT/US 99/26795

Patent document cited in search report	Publication date	Patent family member(s)		Publication date	
EP 0241578	A	WO	8706120 A	22-10-1987	
		US	5443950 A	22-08-1995	
		US	5962325 A	05-10-1999	
		US	5460939 A	24-10-1995	
		US	5510254 A	23-04-1996	
		US	6022743 A	08-02-2000	
		US	5580781 A	03-12-1996	
		US	5516680 A	14-05-1996	
		US	5512475 A	30-04-1996	
		US	5541107 A	30-07-1996	
		US	5516681 A	14-05-1996	
		US	5578485 A	26-11-1996	
		US	5785964 A	28-07-1998	
		US	5518915 A	21-05-1996	
		US	5624840 A	29-04-1997	
		US	5902741 A	11-05-1999	
		US	5863531 A	26-01-1999	
		US	5266480 A	30-11-1993	
		US	5160490 A	03-11-1992	
		US	5849588 A	15-12-1998	
		US	5858721 A	12-01-1999	
US 5580781	A	03-12-1996	US	5443950 A	22-08-1995
			US	5266480 A	30-11-1993
			US	5032508 A	16-07-1991
			US	4963489 A	16-10-1990
			US	4721096 A	26-01-1988
			US	5962325 A	05-10-1999
			US	5460939 A	24-10-1995
			US	5510254 A	23-04-1996
			US	6022743 A	08-02-2000
			US	5516680 A	14-05-1996
			US	5512475 A	30-04-1996
			US	5541107 A	30-07-1996
			US	5516681 A	14-05-1996
			US	5578485 A	26-11-1996
			US	5785964 A	28-07-1998
			US	5518915 A	21-05-1996
			US	5624840 A	29-04-1997
			US	5902741 A	11-05-1999
			US	5863531 A	26-01-1999
			US	5849588 A	15-12-1998
			US	5858721 A	12-01-1999
			AU	644578 B	16-12-1993
			AU	4211489 A	02-04-1990
			BR	8907642 A	20-08-1991
			CA	1335657 A	23-05-1995
			DK	40591 A	07-05-1991
			EP	0358506 A	14-03-1990
			HU	56393 A	28-08-1991
			IL	91536 A	31-10-1996
			JP	4501657 T	26-03-1992
			KR	156571 B	15-10-1998
			KR	156684 B	15-10-1998
			KR	156685 B	15-10-1998
			NO	910787 A	22-04-1991
			NZ	230572 A	23-12-1993
			PT	91676 A	30-03-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Application No.

PCT/US 99/26795

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5580781	A	WO	9002796 A	22-03-1990
		US	5160490 A	03-11-1992
		ZA	8906886 A	27-06-1990
		AT	127692 T	15-09-1995
		AU	6815990 A	14-03-1991
		AU	6816090 A	14-03-1991
		AU	615414 B	03-10-1991
		AU	7356887 A	09-11-1987
		BG	51337 A	15-04-1993
		BR	8707673 A	15-08-1989
		CA	1310926 A	01-12-1992
		DE	3751519 D	19-10-1995
		DK	665687 A	17-12-1987
WO 9015877	A	27-12-1990	AT 148502 T	15-02-1997
			CA 2062741 A	16-12-1990
			DE 69029856 D	13-03-1997
			DE 69029856 T	04-09-1997
			DK 477290 T	21-07-1997
			EP 0477290 A	01-04-1992
			EP 0753574 A	15-01-1997
			ES 2097149 T	01-04-1997
			JP 4506153 T	29-10-1992
			US 5437994 A	01-08-1995
			US 5459069 A	17-10-1995
			US 5763266 A	09-06-1998
			US 5635386 A	03-06-1997
			US 5605822 A	25-02-1997
			US 5670147 A	23-09-1997
			US 5670351 A	23-09-1997
			US 5646043 A	08-07-1997
			US 5888807 A	30-03-1999
			US 5399493 A	21-03-1995